Antiarrhythmic Activity of Befol, Suphan, Mexidol, and T3-146 in Combination with Some Antiarrhythmics

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Antidepressant befol, nonglycoside cardiotonic suphan, succinate-containing synthetic antioxidant mexidol, and pyracetam structural analogue T3-146 were shown to possess antiarrhythmic activity and to potentiate antiarrhythmic effects of bonnecore, obsidan, amiodarone, isoptin, and richlocaine.

Key Words: *befol; suphan; mexidol; T3-146; antiarrhythmics; potentiation*

Cardiac arrhythmias are widespread and characterised by complexity and variety of forms. Most antiarrhythmic drugs produce adverse effects, sometimes dangerous [10]. Therefore, it seems essential to produce acting on primary components of arrhythmogenesis.

Recently, some drugs, such as antidepressant befol (4-chlorine-3-morpholinopropyl-benzamide hydrochloride) [3], nonglycoside cardiotonic suphan (dipotassium salt of N-succinyl-dl-tryptophan) [5], mexidol, a synthetic antioxidant from the group of derivatives of 3-oxypyridine (succinate-containing analogue of emoxypinum) [1], as well as substance T3-146, a cyclic derivative of γ-aminobutyric acid (malate-containing analogue of pyracetam) [4] exhibit antiarrhythmic and antifibrillation activities, and produce antianginal and antihypoxic effects. In addition, they could stabilize the hemodynamic parameters in acute myocardial ischemia.

The development of ischemic heart disease may often be accompanied by "postischemic reperfusion syndrome", which threatens with arising of arrhythmias followed by lethal ventricular fibrillation (VF) [11]. Therefore, special attention was paid to comparison of cardiotonic properties of the above-mentioned drugs and "classical" antiarrhythmics in conditions of coronary artery reperfusion. Taking into account a possible potentiation of beneficial effects of drugs due to interfering with different links of pathological process, it was important to assess the efficacy of combination of "classical" antiarrhythmics with the drugs of metabolic type of action.

In this work we studied antiarrhythmic and antifibrillation activities of befol, suphan, mexidol, and T3-146 in the models of early occlusion (OA) and reperfusion arrhythmias (RA), including VF, as well as their effect on activities of antiarrhythmics of different groups according to conventional classification [15]: bonnecore (IC), obsidan (II), amiodarone (III), isoptin (IV), and a new local anesthetic richlocaine (benzoic ether 1-allyl-2,5-dimethylpiperidol-4 hydrochloride), a potent antiarrhythmic with both IB and IV types of action [7].

MATERIALS AND METHODS

Experiments were carried out on 160 outbred cats, weighing 2.6-3.4 kg.

Cats were narcotised with intraperitoneal sodium ethaminal (40 mg/kg). The left descending branch of the coronary artery was occluded for 30 min and reperfused for 10 min of observation at the level of inferior margin of the auricula atrii under opened thorax and artificial ventilation conditions. Five-

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seven minutes prior to coronary artery occlusion, the drugs and their combinations were slowly injecting intravenously. When injecting pairs of drugs, first a metabolic drug (befol, suphan, mexidol, or T-146) was injected, which was followed by an antiarrhythmic (bonnecore, obsidan, amiodarone, isoptin, or richlocaine) after 5 min.

In order to evaluate antiarrhythmic and antifibrillation activities of the drugs, the number of OA, RA and VF were recorded in an EKIT-04 electrocardiograph.

The results were statistically analysed using χ^2-test [2].

RESULTS

In the control series of experiments, ligation of coronary artery induced OA in 100% of cases, 25% of which transferring to lethal VF. Subsequent coronary artery reperfusion was followed by RA in all animals (100%), with VF in 67%.

Then we determined the effective doses of the antiarrhythmics for statistically significant prevention of OA, RA, and VF. For bonnecore, obsidan, amiodarone, isoptin, and richlocaine they were: 2, 2, 5, 0.8, and 5 mg/kg, respectively. For the metabolic drugs (befol, suphan, mexidol, and T3-146) these doses were: 20, 45, 50, and 50 mg/kg, respectively.

In order to reveal a potentiating effect during combined action of drugs, they were given in subthreshold (noneffective or slightly effective) doses, which were a half of the effective doses. The most pronounced effects were observed when metabolic drugs were combined with bonnecore. In all experiments, no OA were observed, except 1 of 7 (14%) in the series with combination of bonnecore and T3-146. A decrease in RA rate was also significant (17-43%, compared with 100% in the control). There were no VF in the series with combined application of bonnecore with suphan or mexidol, and very few in the case of combinations with befol and T3-146 (17 and 14% against 67% in the control).

Similar results were obtained for richlocaine applied against the background of metabolic drugs. Statistically significant decrease in the rates of OA, RA, and VF was observed in all cases, though this was less notable than in case of bonnecore. In the given series of experiments, the most efficient was the mexidol+richlocaine combination, which prevented OA and VF in 100%, and RA in 50% of cases.

When given with metabolic drugs (both in subthreshold doses), obsidan exhibited high antiarrhythmic activity. For befol, suphan, or T3-146 given as a background, OA and RA occurred in 33 and 50% of cases, respectively.

For mexidol these values fell to 17 and 33%, respectively. Statistically significant antifibrillatory effect was produced by all combinations, except obsidan+befol (for which VF took place in 50% of animals).

Under the action of amiodarone combined with befol or mexidol the percentage of OA decreased to 33%, and with suphan to 17%. Significantly lesser numbers of RA and VF were encountered under amiodarone in combination with befol, suphan, or T3-146 (17 and 17%, 50 and 17%, 17 and 17%, respectively). Combination of amiodarone with mexidol appeared to be ineffective in respect to RA and VF.

The study of antiarrhythmic activity of combinations of isoptin with befol or T3-146 under conditions of OA, RA, and VF revealed potentiation of their effects. When the antiarrhythmic was applied with befol, arrhythmias (VF including) occurred in 1 of 6 animals (17%). With T3-146 taken as a background, OA were absent in all animals, and RA and VF were found in 33 and 17% of cats, respectively. The isoptin+mexidol combination was effective against OA and RA (33 and 50%, respectively), but not against fibrillation. By contrast, isoptin+suphan combination produced a significant antifibrillation effect and was ineffective against OA and RA.

According to modern theory, the main factors responsible for damaging action of reperfusion are cardiotoxic effect of free oxygen radicals and overload of cardiomyocytes with Ca^{2+} [11]. This implies that the capability of befol, suphan, T3-146, and mexidol to act beneficially on lipid peroxidation [4,9,14] plays an important role in their cardioprotective action. Moreover, befol, suphan, and mexidol affect Ca-homeostasis in cardiomyocytes. Thus, suphan enhances accumulation of Ca^{2+} in the sarcoplasmic reticulum by transferring them into depot [6]. Cardiotonic effect of befol is due to its predominant effect on Na/ Ca^{2+}-exchange [12]. In conditions of lipid peroxidation, the antioxidant mexidol stabilizes the lipid bilayer of the cardiomyocyte sarcollema and limits transmembrane influx of extracellular Ca^{2+} [1]. It cannot be excluded that such an inhibitory action on lysosome enzymes (cathepsin D and β-glucosidase) and ability of T3-146, suphan, and befol to prevent destruction of cardiomyocyte ultrastructure in acute myocardial hypoxia [13,14] also contribute to their cardiotonic effect.

Thus, application of drugs with metabolic type of action in combination with antiarrhythmics of different types to prevent arrhthmiasof either ischemic or reperfusion genesis markedly enhances both the effectiveness and safety of antiarrhythmic therapy. The mechanism of potentiation of their activity

Table 1. The Effect of Bonnecore, Obsidan, Amiodarone, Isoptin, Richlocaine, Befol, Suphan, Mexidol, and T3-146 and their Combinations on Early Occlusion and Reperfusion Arrhythmias in Cats

Preparations and their combinations	Dose, mg/kg	Number of animals					
		with occlusion			with reperfusion		
		experiment	arrhythmia	fibrillation	experiment	arrhythmia	fibrillation
Control		24	24 (100)	6 (25)	18	18 (100)	12 (67)
Bonnecore	2.0	6	1 (17)*	0 (0)	6	1 (17)*	0 (0)*
Obsidan	2.0	8	5 (63)*	0 (0)	8	5 (63)*	2 (25)*
Amiodarone	5.0	10	6 (60)*	0 (0)	10	5 (50)*	3 (30)*
Isoptin	0.8	10	6 (60)*	0 (0)	10	5 (50)*	3 (30)*
Richlocaine	5.0	10	3 (30)*	0 (0)	10	4 (40)*	2 (20)*
Befol	20.0	7	2 (29)*	0 (0)	7	2 (29)*	0 (0)*
Suphan	45.0	7	3 (43)*	0 (0)	7	2 (29)*	0 (0)*
Mexidol	50.0	6	3 (50)*	0 (0)	6	3 (50)*	3 (50)
T3-146	50.0	10	3 (30)*	0 (0)	10	1 (10)*	1 (10)*
Befol+Bonnecore	10.0+1.0	6	0 (0)*	0 (0)	6	1 (17)*	1 (17)*
Suphan+Bonnecore	22.5+1.0	6	0 (0)*	0 (0)	6	2 (33)*	0 (0)*
Mexidol+Bonnecore	25.0+1.0	6	0 (0)*	0 (0)	6	1 (17)*	0 (0)*
T3-146+Bonnecore	25.0+1.0	7	1 (14)*	0 (0)	7	3 (43)*	1 (14)*
Befol+Obsidan	10.0+1.0	6	2 (33)*	0 (0)	6	3 (50)*	3 (50)
Suphan+Obsidan	22.5+1.0	6	2 (33)*	0 (0)	6	3 (50.)*	1 (17)*
Mexidol+Obsidan	25.0+1.0	6	1 (17)*	0 (0)	6	2 (33)*	1 (17)*
T3-146+Obsidan	25.0+1.0	6	2 (33)*	0 (0)	6	3 (50)*	1 (17)*
Befol+Amiodarone	10.0+2.5	6	2 (33)*	0 (0)	6	1 (17)*	1 (17)*
Suphan+Amiodarone	22.5+2.5	6	1 (17)*	0 (0)	6	3 (50)*	1 (17)*
Mexidol+Amiodarone	25.0+2.5	6	2 (33)*	0 (0)	6	4 (67)	2 (33)
T3-146+Amiodarone	25.0+2.5	6	1 (17)*	0 (0)	6	1 (17)*	1 (17)*
Befol+Isoptin	10.0+0.38	6	1 (17)*	0 (0)	6	1 (17)*	1 (17)*
Suphan+Isoptin	22.5+0.38	6	5 (83)	0 (0)	6	5 (83)	1 (17)*
Mexidol+Isoptin	25.0+0.38	6	2 (33)*	0 (0)	6	3 (50)*	2 (33)
T3-146+Isoptin	25.0+0.38	6	0 (0)*	0 (0)	6	2 (33)*	1 (17)*
Befol+Richlocaine	10.0+2.5	6	2 (33)*	0 (0)	6	3 (50)*	1 (17)*
Suphan+Richlocaine	22.5+2.5	7	1 (14)*	0 (0)	7	4 (57)*	1 (14)*
Mexidol+Richlocaine	25.0+2.5	6	0 (0)*	0 (0)	6	3 (50)*	0 (0)*
T3-146+Richlocaine	25.0+2.5	6	2 (33)*	0 (0)	6	3 (50)*	1 (17)*

Note: percentage is given in parentheses; *$p<0.05$ compared with control.

consists in simultaneous action of drug components on different components of arrhythmia pathogenesis.

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